FORM P1

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

PATENT APPLICATION AND ACKNOWLEDGEMENT

[Section 30(1) - Regulation 22]

The grant of a patent is hereby requested by the undermentioned applicant on the basis of the present application filed in duplicate.

21	01	Official Application No. 2001/10500
71		Full name(s) and address(es) of applicant(s):

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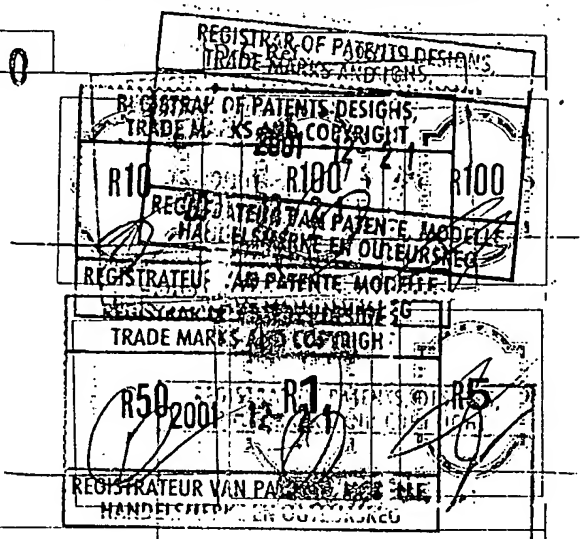

54	Title of invention:	

PHARMACEUTICAL COMPOSITION

X	The applicant claims priority as set out on the accompanying form P2. The earliest priority claimed is: 11 May 2001 ZA 2001/3832			
	This application is for a patent of addition to Patent Application No.	21	01	
	This application is a fresh application (section 37) based on Application No.	21	01	

THIS APPLICATION IS ACCOMPANIED BY THE FOLLOWING:

☐	1.	P6	Provisional specification	Pages:	
☒		P7	Complete specification	Pages: 13	2 copies
☐	2.		Drawings	Sheets:	
☒	3.	P8	Publication particulars and abstract in duplicate.		
☐	4.		Drawing for abstract		
☒	5.		An assignment of invention		
☐	6.		Certified priority document(s)		
☒	7.		Copy of Form P2 and SA Patent Application No		
☐	8.		Translation of the priority document(s)		
☐	9.		An assignment of priority rights		
☐	10.	P3	Declaration and power of attorney on form P3		
☐	11.	P4	Request for ante-dating on form P4		
☐	12.	P4	Request for classification on form P9		
☒	13.	P2	Register sheet (in duplicate)		

21	01	ZA 2001/3832

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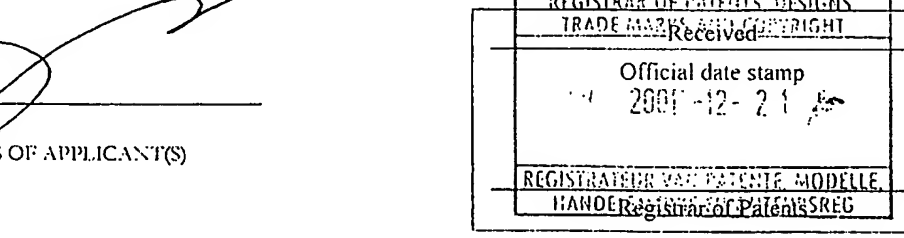

FORM P7

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

COMPLETE SPECIFICATION

[Section 30(1) - Regulation 28]

21	01	Official Application No: 2001/10500	DrG Ref.: 596714
22		Lodging date: 2001-12-21	
51		International Classification: A61K	

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54 **Title of invention:**
PHARMACEUTICAL COMPOSITION

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TITLE OF INVENTION

Pharmaceutical composition.

FIELD OF INVENTION

The present invention relates to pharmaceutical compositions for treating human immunodeficiency virus (HIV) infections.

BACKGROUND TO INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome or AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III or ARV.

A common feature of retrovirus replication is the extensive post-translation processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. Inhibition of this processing prevents the production of normally infectious virus. For example, *Kohl, N.E. et al., Proc. Nat'l Acad. Sci., 85, 4686 (1988),* demonstrated that genetic inactivation of the HIV encoded protease resulted in the production of immature, non-infectious virus particles. These results indicate that inhibition of the HIV protease represents a viable method for the treatment of AIDS and the prevention or treatment of infection by HIV.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame *[Ratner, L. et al., Nature, 313, 277 (1985)].* Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, an endonuclease and an HIV protease *[Toh, H. et al., EMBO J., 4,*

1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)].

One substantial and persistent problem in the treatment of AIDS has been the ability of the HIV virus to develop resistance to the individual therapeutic agents employed to treat the disease. Thus, a need remains for an efficacious and long lasting therapy for AIDS which lowers HIV viral levels of patients to undetectable levels and raises CD4 cell counts for prolonged periods of time without the development of resistance.

It is an object of the invention to provide a pharmaceutical composition which, inter alia, will assist in treating the human immunodeficiency virus (HIV) infections.

SUMMARY OF INVENTION

According to the invention, a pharmaceutical composition, includes in combination Lamivudine, Zidovudine and Nevirapine, or pharmaceutically acceptable derivatives thereof.

The composition may be provided as a tablet.

The composition may include about 100 to 150 mg lamivudine per unit dosage form.

The composition may include 150 mg lamivudine per unit dosage form.

The composition may include about 200 to 600 mg Zidovudine per unit dosage form.

The composition may include 300 mg stavudine per unit dosage form.

The composition may include about 150 to 250 mg nevirapine per unit dosage form.

The composition may include 200 mg nevirapine per unit dosage form.

The composition may be provided in the form of a coated tablet having a tablet core and a coating.

The active ingredients evenly dispersed through the tablet core.

The composition may include an effective amount of disintegrant.

The composition may include an effective amount of diluent, such as microcrystalline cellulose, lactose, starch, dicalcium phosphate, typically an effective amount comprises 45 % to 50 % of the formulation.

The composition may include lubricants, such as magnesium stearate, zinc stearate, calcium stearate, magnesium oxide and more preferably magnesium stearate, added at a level of from 0,5 to 1.0 %.

The composition may substantially include the following ingredients in mg per unit dosage form:

Lamivudine	150.0
Zidovudine	300.0
Nevirapine	200.0
Microcrystalline cellulose	350.0
Sodium starch glycollate	12.0
Magnesium stearate	6.0
Talc	6.0
Colloidal Silicon dioxide	6.0

Coat:

Hydroxypropyl cellulose	11.6
Polyethylene glycol 6000	2.4
Solvent	q.s.

Also according to the invention, a method of preparing a pharmaceutical composition, includes the steps of blending a diluent with Lamivudine, Zidovudine and Nevirapine; of granulation thereof with water into granules; of drying the resulting granules and sizing; of blending the granules with disintegrant; of lubricating the granules; and of compressing the lubricated granules into tablets.

The method may include the step of suitably coating the tablets.

Yet further according to the invention, a method for treating reversing, reducing or inhibiting retroviral infections, in particular HIV infections in a human, includes administering to a mammal a safe and effective amount of the pharmaceutical composition as hereindescribed.

Yet further according to the invention, the use of a composition for the treatment of viral infections, particularly retroviral infections, including human immunodeficiency virus (HIV) infections.

Reference herein to "treatment" as used herein is to extend to both the prophylaxis and the treatment of an establishd malady, infection or its symptoms.

HIV causes a variety of clinical conditions including acquired immunodeficiency syndrome (AIDS) and chronic neurological disorders. Multiple-drug treatment regimens dramatically improve the treatment of HIV infected patients. Prior to these multiple-drug regimens, treatment was often limited to single drugs with limited effectiveness.

Single drug treatment regimens typically require long-term treatment increasing the incidence of unwanted side effects. Moreover, single drug therapies are particularly vulnerable to mutation in the HIV virus, leading to drug-resistant variants of HIV.

The use of multiple drug therapies may reduce the development of drug resistant strains of HIV because one drug will usually cancel out mutations against other drugs. Multiple-drug therapies may even inhibit replication of HIV viruses for a period of time sufficient to eliminate HIV from the body.

The success of modern multiple drug treatments for HIV often requires strict compliance with a complex treatment regiment that can require the administration of many different drugs per day, administered at precisely times intervals with careful attention to diet. Patient non-compliance is a well known problem accompanying such complex treatment regimens. (See *Goodman and Gilman, the pharmacological basis of therapeutics, 9th edition pp. 1704-1705 (1998)* incorporated herein by reference.) Patient non-compliance is an important problem in the treatment of HIV because such non-compliance may lead to the emergence of multiple drug resistant strains of HIV.

This combination therapy in accordance with the invention provides a method to enhance the effectiveness in treating AIDS and to preclude the development of resistance to the individual therapeutic agents.

Lamivudine (also known as 3TC) is a synthetic nucleoside analogue, chemically known as (2R, cis)-4-ammino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is commercially available from *Glaxo Wellcome Inc* under trade name *EPIVIR*. Lamivudine and its use against HIV are described in WO 92/21676.

US Pat. No. 5,047,407 discloses (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-)1H)-pyrimidin-2-one *(Epivir. RTM., Lamivudine)* and its use in the treatment and prophylaxis of viral infections. Lamivudine has proven anti-viral activity against HIV and other viruses such as HBV.

Nevirapine or 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b: 2',3'-e][1,4]diazepin-6-one, is a known agent for the treatment of infection by HIV-1

(human immunodeficiency virus type1), which acts through specific inhibition of HIV-1 reverse transcriptase. Its synthesis and use are described in various publications including, inter alia, U.S. Pat. No. 5,366,972; European Patent Application No. 0 429 987, U.S. patent application Ser. No. 08/515,093 and U.S. patent application Ser. No. 08/371,622. Viramune.RTM. tablets, a pharmaceutical comprising Nevirapine in tablet form, has recently been approved by the U.S. Food and Drug Administration for use in the treatment of HIV-1 infection.

Zidovudine chemically known as 3'-azido-3'-deoxythymidine, is now well established as an important and useful chemotherapeutic agent for the treatment and/or prophylaxis of HIV -infections including related clinical conditions such as AIDS, AIDS-related complex (ARC, AIDS dementia) complex (ADC) and also for the treatment of patients who have an asymptomatic HIV infection of who are anti-HIV antibody -positive. Zidovudine is a pyrimidine nucleoside analogue commercially available from *Glaxo Wellcome Inc.* under the trade mark *Retrovir*™ for treatment of HIV as described in US patent 4,818,538, 4,828,838, 4,724,232 and 4,833,130. Methods of preparation of Zidovudine are described in US patent no. 5,011,828.

By means of the pharmaceutical composition in accordance with the invention treatment regimens for HIV and other viruses can be simplified with the goal of enhancing patient compliance by providing a simplified dosage form containing a combination of pharmaceutically acceptable amounts of Lamivudine, Stavudine and Nevirapine or pharmaceutically acceptable derivatives thereof.

The phrase 'safe and therapeutically effective amount' as used herein is intended to refer to a sufficient amount of a drug, compound, composition, product or pharmaceutical agent to abate or reverse or treat a malady in human

or other mammal without severely harming the tissues of the mammal to which the drug or pharmaceutical agent is administered.

The phrase 'pharmaceutically acceptable derivative' as used herein is intended to any pharmaceutically acceptable salt, solvent, ester or salt of such ester, or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) the intended active ingredient or any active metabolite or residue thereof.

The pharmaceutical composition of the invention employs a combination safe and therapeutically effective amount of two or more therapeutically active agents viz. safe and therapeutically effective amounts of Nevirapine, or 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b: 2',3'-e][1,4] diazepin-6-one and its pharmaceutically acceptable salts, solvents and derivatives thereof, a safe and therapeutically effective amounts (-)2',3'-dioxy,3'-thyacytidine (Lamivudine) and its pharmaceutically acceptable salts, solvents and derivatives thereof, a safe and therapeutically effective amounts of Zidovudine (3'-azido-3'-deoxythymidine) and its pharmaceutically acceptable salts, solvents and derivatives thereof along with a safe and effective amount of pharmaceutically acceptable excipients to maintain the composition's homogeneity prior to tablet compression.

The pharmaceutical composition of the present invention conveniently allows administration of three separate active compounds in unit dosage form containing

- Lamivudine of about 100 -150 mg and more particularly 150 mg per unit dosage form;
- Stavudine of about 15 - 40 mg and more particularly 40 mg per unit dosage form; and

- Zidovudine of about 200-600 mg and more particularly 300 mg per unit dosage form

The composition may optionally employ a combination of two or more active agents along with a safe and effective amount of a diluent, a safe and effective amount of disintegrant and a safe and effective amount of a lubricant or any other safe and effective amount of excipients commonly used in the art.

The composition may be in the form of coated tablets. The tablet may be coated according to any method known to person skilled in the art that would not interfere with tablet release properties, or other physical and chemical characteristics of the invention. The coated tablet contain the active ingredients that are evenly dispersed through the tablet core.

The composition may also include an effective amount of diluent such as microcrystalline cellulose, lactose, starch, dicalcium phosphate, typically an effective amount comprises 45 % to 50 % of the formulation.

Preferably lubricants, such as magnesium stearate, zinc stearate, calcium stearate, magnesium oxide and more preferably magnesium stearate, may be added at a level of from 0,5 to 1.0 %.

DESCRIPTION OF EXAMPLE

The following example further describes a pharmaceutical composition in accordance with the present invention.

Example

Pharmaceutical composition of conventional tablet containing Lamivudine, Zidovudine and Nevirapine.

Ingredient	mg/tablet
Lamivudine	150.0
Zidovudine	300.0
Nevirapine	200.0
Microcrystalline cellulose	350.0
Sodium starch glycollate	12.0
Magnesium stearate	6.0
Talc	6.0
Colloidal silicon dioxide	6.0

Film coat:

Hydroxypropyl cellulose	11.6
Polyethylene glycol 6000	2.4
Solvent	q.s.

Manufacturing process involved blending or diluent with Lamivudine, Nevirapine and Zidovudine followed by granulation with water. The granules were dried, sized, blended with disintegrant and then lubricated. The lubricated blend were then compressed.

PATENT CLAIMS

1. A pharmaceutical composition, includes in combination Lamivudine, Zidovudine and Nevirapine, or pharmaceutically acceptable derivatives thereof.

2. A composition as claimed in claim 1, which is provided as a tablet.

3. A composition as claimed in any one of the preceding claims, which includes about 100 to 150 mg lamivudine per unit dosage form.

4. A composition as claimed in claim 3, which includes 150 mg lamivudine per unit dosage form.

5. A composition as claimed in any one of the preceding claims, which includes about 200 to 600 mg Zidovudine per unit dosage form.

6. A composition as claimed in claim 5, which includes 300 mg stavudine per unit dosage form.

7. A composition as claimed in any one of the preceding claims, which includes about 150 to 250 mg nevirapine per unit dosage form.

8. A composition as claimed in claim 7, which includes 200 mg nevirapine per unit dosage form.

9. A composition as claimed in any one of the precedings claims, which is provided in the form of a coated tablet having a tablet core and a coating.

10. A composition as claimed in claim 9, in which active ingredients are evenly dispersed through the tablet core.

11. A composition as claimed in any one of the preceding claims, which includes an effective amount of disintegrant.

12. A composition as claimed in any one of the preceding claims, which includes an effective amount of diluent, such as microcrystalline cellulose, lactose, starch, dicalcium phosphate, typically an effective amount comprises 45 % to 50 % of the formulation.

13. A composition as claimed in any one of the preceding claims, which includes lubricants, such as magnesium stearate, zinc stearate, calcium stearate, magnesium oxide and more preferably magnesium stearate, added at a level of from 0,5 to 1.0 %.

14. A composition as claimed in any one of the preceding claims, which substantially includes the following ingredients in mg per unit dosage form:

Lamivudine	150.0
Zidovudine	300.0
Nevirapine	200.0
Microcrystalline cellulose	350.0
Sodium starch glycollate	12.0
Magnesium stearate	6.0
Talc	6.0
Colloidal Silicon dioxide	6.0

Coat:

Hydroxypropyl cellulose	11.6
Polyethylene glycol 6000	2.4
Solvent	q.s.

15. A method of preparing a pharmaceutical composition, which includes the steps of blending a diluent with Lamivudine, Zidovudine and Nevirapine; of granulation thereof with water into granules; of drying

the resulting granules and sizing; of blending the granules with disintegrant; of lubricating the granules; and of compressing the lubricated granules into tablets.

16. A method as claimed in claim 15, which includes the step of suitably coating the tablets.

17. A method for treating reversing, reducing or inhibiting retroviral infections, in particular HIV infections in a human, which method includes administering to a mammal a safe and effective amount of the pharmaceutical composition as claimed in any one of claims 1 to 14.

18. Use of a composition as claimed in any one of claims 1 to 14, for the treatment of viral infections, particularly retroviral infections, including human immunodeficiency virus (HIV) infections.

19. A pharmaceutical composition substantially as hereinbefore described.

20. A method of preparing a pharmaceutical composition substantially as hereinbefore described.

21. A method for treating reversing, reducing or inhibiting retroviral infections substantially as hereinbefore described.

22. Use of a composition substantially as hereinbefore described.

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